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PHARMACOKINETIC BASIS OF AGE-RELATED CHANGES IN SENSITIVITY TO TOXICANTS[1]

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INTRODUCTION

The elderly represent the fastest growing segment of the population in the United States and other developed countries. Demographic studies estimate that 20% of the population will be "elderly", over the age of 65, by the year 2030 (1). This represents a gradual increase from 1950 to 1980 when 8% and 12%, respectively, of the population were 65 or older (2). Those aged 85 and over constitute the fastest growing segment of the population and this segment is expected to triple between 1980 and 2020 (3). In fact, a life expectancy of 81 years for females and 73 years for males appears likely within the next 10 years (4).

Since the elderly have the highest incidence of illness, they require a disproportionate share of health care services. As an example, the elderly as a group are the major users of prescription drugs (5). The incidence of idiosyncratic or adverse drug reactions in this group is elevated as compared to the general population (6–8). While this may be due in part to issues of polypharmacy and compliance (9, 10), both the nature of drug response as well as the frequency of adverse drug reactions clearly increase with age (11,

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12). Age-related changes in clinical pharmacology have been reviewed extensively (5, 13–17).

In contrast, little effort has been made to investigate alterations in toxicological responses of the elderly, specifically in regard to environmental chemicals. The perception of altered sensitivity of the elderly to environmental insults is based largely on the enhanced incidence of adverse or unpredictable drug reactions as discussed above. In other words, the elderly have been viewed as a population at special risk to environmental insult due to their enhanced sensitivity.

Environmental agents can play a more subtle and difficult-to-define role in relation to the elderly. Environmental insults can, in theory, also modulate the very processes of aging, few of which have been unequivocally identified (18). Conceptually, any number of environmental agents can interfere with the process of aging, whether programmed or stochastic (19). Generally, environmental insults are perceived as life-shortening events, hastening the onset or increasing the progression of "normal" age-related changes. In fact, there are several well-documented examples of environmental alterations of the aging process. The best described is photoaging of the skin, where it has only been recently possible to distinguish between UV-induced changes and intrinsic aging using ultrastructural techniques (20). Premature aging of the lungs can result from air pollution. Recent epidemiology studies have indicated that chronic exposure to elevated levels of ozone causes decrements in lung function that normally occur with advancing age (21). Aging of specific areas of the central nervous system appears accelerated by exposure to pyridine-based pesticides and related compounds. For example, an active metabolite of the "designer" drug MPTP selectively destroys neurons in the substantia nigra, resulting in neurologic symptoms that mimic Parkinson's disease (22). Certain genetic disorders such as progeria, a disease that affects children, or Werner's syndrome, which is expressed in young adults, may also moderate the processes of aging. It has been hypothesized that environmental genotoxins could be involved in such genetic alterations.

In contrast to those processes that accelerate aging, only one environmental manipulation has been demonstrated to slow the processes of aging, at least in experimental animals. Dietary restriction appears to retard many of the processes of aging, affecting both the rate of biological aging and the development of age-related diseases (23, 24). For example, restriction of total protein intake significantly reduces the incidence and severity of age-related kidney disease (25).

Environmental insults are continuing to increase. While the US Clean Air Act of 1970 resulted in tighter control of automobile emissions, the great increase in the number of vehicles has compounded the problem in air quality in congested areas. Increasing the height of factory smoke stacks decreased

the level of pollutants in the immediate area but caused pollution to be spread over a much greater distance. Over 50,000 commercial chemicals are produced each year, with little or no toxicity data on the great majority (26).

SENSITIVITY

Age-related changes in sensitivity to environmental chemicals can be due to alterations in either toxicokinetic or toxicodynamic processes, i.e. what the body does to the chemical agent vs what the compound does to the body. The enhanced sensitivity of the elderly to environmental agents and drugs cannot be explained on the basis of either altered disposition or inherent tissue sensitivity alone, but often is due to interactions between these two types of processes. Toxicodynamic changes occurring at the target site may involve changes in cell populations, cellular receptors, cellular responsiveness, or in amount and/or activity of both informational and structural cellular macromolecules. Aging can alter the synthesis, degradation, and regulation of such molecules, resulting in altered responses in the aged. For example, altered receptor sensitivity towards many drugs, including cardiac glycosides, benzodiazepines, tricyclic antidepressants, and the nonsterodial anti-inflammatory agents has been demonstrated in the aged (27, 28).

In fact, many pharmacodynamic changes observed in the elderly are due to alterations in receptor numbers or functions (29). Steroid responsiveness appears to decline with age. Not only does estrogen receptor concentration decrease (30), but its nuclear translocation also appears reduced (31). Post receptor events may also play a role in decreased steroid responsiveness (32). In general, the number of receptors for steroids, insulin, glucagon, and prolactin appear to decrease in aging rodents, dogs, and humans (33).

The situation in adrenergic receptors is more complex. The decline in beta adrenergic responsiveness is well documented in the elderly (34, 35). This could in part relate to decreased synthesis of norepinephrine (36). In the brain, reduced responsiveness to catecholamines appears due to a decline in the affinity of the β-adrenergic receptors without any change in receptor number (37). This also appears to be the case in lymphocytes (38). Aging does not, however, impair the ability of β-adrenoreceptors to be up-regulated following chemical denervation (39). Beta-adrenergic signalling may also be affected by age (40, 41).

Alpha adrenergic responsiveness has also been reported to decline with age (42). Whether this is due to changes in α-adrenergic receptor numbers or affinity is not known. However, the impaired responsiveness may be due, at least in part, to an age-related defect in the ability of inositol triphosphate to release calcium from intracellular sites, i.e. a postreceptor signalling defect

(43). Enhanced sensitivity of the elderly to benzodiazepines may also be due to changes distal to the receptor (44).

Decreased responsiveness to other neurotransmitters has also been reported in the elderly. Decreases in both serotonin and dopamine receptors occur in rats and humans (45–47). Similarly, the number of opiate receptors appears to decrease with age (48). These neurological changes could clearly affect behavioral alterations observed in the elderly.

Age-related changes in tissue sensitivity to other agents have been reported. For example, nonsteroidal antiinflammatory agents appear to cause more side effects in stomach, kidney, bone marrow, and brain of the elderly than in young patients (49). The stomach, liver, testes, brain, and kidneys of aged rats demonstrated enhanced sensitivity to 2,2,2-trifluoroethanal, the toxic metabolite of fluroxene (50). Aging liver appears to have enhanced susceptibility to ethanol toxicity (51). The aging heart is more sensitive to ouabain (52) and intravenous anesthetics (53), while the aging brain has enhanced sensitivity to nitrazepines (15). In fact, enhanced sensitivity to such diverse central nervous depressants as phenobarbital and hexobarbital (54), phenytoin (55), and oxazepam (56) appears to be a general change occurring during brain aging.

The aging kidney also appears to be more susceptible to nephrotoxic insult than kidneys from younger organisms. Senescent rats are more sensitive to renal ischemia than young rats (57). An increased incidence of adverse renal reactions to acetaminophen has also been reported in the elderly (58). This may be due to an innate increase in susceptibility of the proximal tubules (59). Enhanced cephaloridine toxicity may be due to changes in active transport of organic ions in the aging renal cortex (60). In contrast, there appears to be an age-related decrease in hydrocarbon-induced hyaline droplet nephropathy (61). This lack of sensitivity is due to the age-dependent decline in synthesis of α_{2u}-globulin (62), which is strongly associated with hyaline droplet formation.

While toxicodynamic changes occurring with age result in altered tissue sensitivity, many age-related differences in drug responsiveness appear to have a toxicokinetic basis. Toxicokinetics, like pharmacokinetics, describes the processes of absorption, distribution, metabolism, and excretion of drugs or other chemicals in the body. Many of the physiological and biochemical changes that occur during aging can modulate any of these aspects of disposition, leading to an altered dose to the target tissue and potentially an altered response. Since age-related changes in the pharmacokinetics of drugs, carcinogens, and other xenobiotics have been recently reviewed (5, 63–72), this manuscript focuses on recent experimental studies involving chemicals of environmental interest.

ABSORPTION

For environmental chemicals there are three major portals of entry—the skin, respiratory tract, and gastrointestinal tract. Alterations in the structure and function of these organ systems clearly occur with age, affecting their absorptive capacities.

Very little is known about age-related changes in pulmonary absorption. Pulmonary function declines continuously with age (73). This is especially true of the function of small airways (74). Respiratory efficiency declines in aging rodents, dogs, and humans (75–77). The rate of gas exchange from the alveoli into the pulmonary capillaries is also reduced (76). These functional changes occur in the absence of obvious structural differences in aging lung (78). No measurements of actual pulmonary uptake in aging vs young organisms have been conducted.

Percutaneous absorption can be an extremely important route of exposure to environmental chemicals. Skin structure changes throughout life (79), although many alterations may result from exposure to sunlight rather than from intrinsic aging (20). In humans, skin thickness increases during maturation and then gradually declines (80). However, the barrier function of skin does not appear to be compromised by this thinning (81). In rodents, skin thickness also increases during development, but shows no significant age-related decline past maturity (82).

The most dramatic age-related changes in dermal absorption occur during development, and most likely reflect the structural changes occurring during this period. Infant skin is more permeable than that of any other age group (79). Recent studies (83) comparing weanling to young adult rats noted a twofold decrease during maturation in the dermal absorption of the highly toxic environmental compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). A further decrease occurred between young adulthood (2–3 months of age) and middle age (19 months), with no further changes occurring during senescence (24 months) (84). Similar results were obtained with the related chemical, 2,3,4,7,8-pentachlorodibenzofuran (4PeCDF) (84), Evans blue dye (85), and straight chain alcohols and hydrocortisone (86). This postmaturational decline in percutaneous absorption has also been observed in humans where a 67% decrease in the dermal absorption of testosterone between young (24 years) and old (75 years) volunteers has been observed (87). Similar results have been reported for benzoic acid (88) and tri-n-propylphosphate (89). In contrast, other studies have observed increases in dermal absorption with age (90, 91). The basis for these age-related declines in dermal absorption remains unclear. Christophers & Kligman (87) suggested these changes were due to alterations in dermal blood flow. Although Yates & Hiley (92)

reported an age-related decrease in blood flow to the skin, Monteiro-Rievere and co-workers (82) failed to detect any postmaturational changes in blood flow. However, blood flow to the skin did decrease during maturation. In addition, age-related alterations in the lipid content (93) and composition (94) of the stratum corneum could play a major role in modulating dermal absorption.

While age-related alterations in gastrointestinal absorption have been studied in greater depth, the situation following oral exposure to environmental toxicants is less clear. There are many, well-documented changes in both the structure and physiology of the gastrointestinal tract occurring with age. These include reductions in gastric acidity, decreased gastric emptying, increased intestinal transit time, and a decreased absorptive surface. A reduction in gastric acid secretion (95, 96) leads to an increase in pH that can alter the ionization of charged compounds, thus affecting their ability to passively diffuse across the gut wall. Decreases in gastric motility in both the small (97) and large intestines (98) can prolong the transit time of chemicals in the gut, thus increasing their potential for absorption. The composition of the small intestine also changes with age. Not only does both the absolute and relative weight of the intestinal mucosa increase (99, 100), but the rate of crypt-cell proliferation also increases in the aging organism (101, 102). In fact, aging is associated with increased gastric mucosal proliferative activity which can be inhibited by epidermal growth factor (103). Splanchnic blood flow decreases (92), due to a reduction in cardiac output (104).

While both pulmonary and dermal absorption solely involve processes of passive diffusion, gastrointestinal absorption can be passive or active, including phagocytosis. Many small molecules, such as simple sugars, amino acids, vitamins, and metal ions, are actively transported across the gut wall. In contrast, most larger molecules and xenobiotics are passively absorbed. No age-related changes have been observed in the oral absorption of a variety of drugs in humans (105–108). Likewise, the oral absorption of TCDD in rats does not change with age (100). Passive absorption of small endogenous molecules such as glucose (109), vitamin A (110, 111), vitamins D, B_{12}, and niacin (110, 112), or many amino acids (113) also fails to show any age-related decline. In contrast, the absorption of both tyrosine (114, 115) and xylose (116) declines with age. The absorption of cholesterol (117) and oleic acid (118) appears to increase with age, perhaps due to changes in the unstirred water layer.

In contrast to passive absorption, active transport appears to decrease with age in both experimental animals and humans. In elderly people the active uptake of galactose, calcium, thiamine, and iron is reduced (15). Active transport of glucose (109, 119, 120) decreases in experimental animals. This appears due to a decrease in the carrier-mediated component of glucose

transport in the brush border membrane of the small intestine (121), and is in agreement with studies using human intestinal tissue (122). Active transport of calcium (123, 124) and phosphorous (123) also declines with age. As with glucose, the decrease in active transport is due to a reduction in the number of calcium carriers in the intestinal membranes (125).

DISTRIBUTION

Once a compound is absorbed into the blood stream, regardless of its portal of entry, it will de distributed throughout the body according to its physicochemical properties and binding characteristics to different constituents. Although the portal of entry affects how much of a compound enters the systemic circulation, it will not alter its future distribution. Lipophilic molecules readily traverse tissue membranes from the blood and accumulate in lipid-rich tissues. Most compounds are not distributed free in solution, but are bound to plasma proteins or cellular constituents. Body composition, macromolecular binding, and blood flow have all been reported to change with age. As previously mentioned, cardiac output declines with age (126), with a resulting decrease in blood flow to the liver, skin, GI tract, and kidneys (92). However, changes in rate of blood flow in skin of aged as compared to young adult rodents have not been found (84). In contrast, recent studies have confirmed the age-related reduction in blood supply to the kidney (127).

Binding to blood proteins can also change with age. There is a significant reduction in plasma albumin in both experimental animals (128, 129), and humans (130, 131). This can lead to an increased free, and hence active, concentration of compounds that are normally highly bound. Clinical sequelae have been demonstrated for a variety of drugs in the elderly (5). Even for a compound that is only partially bound to albumin, such as salicylate, the increase in the free fraction in the elderly can reduce clearance (132). Decreased binding to erythrocytes has also been reported to occur during aging (133), leading to a higher level of free drug.

Probably the most important determinant of age-related alterations in distribution involves changes in body composition. The decrease in lean body mass in both animals (134) and humans (135, 136) has been well documented. There is an increase in the amount of body fat (136) coupled to a loss of body water (137). Such changes can influence the apparent volume of distribution (Vd) of chemicals, thus modulating the concentration at the target site. Thus, for compounds that are relatively water-soluble, such as paracetamol (138) and ethanol (139), the age-related decrease in Vd may result in less extensive distribution and hence a greater concentration at the target tissue. Conversely, for lipophilic compounds such as lignocaine (140) and thiopen-

tone (141) the increase in adipose tissue results in a greater Vd and potentially a lower concentration at the site of action.

Similar changes, and results, occur in animals. Adipose tissue content in young adult rats is generally in the range of 6–12% of body weight (depending on sex and strain). In contrast, fat content of aging Fischer rats may reach 18% (84), while senescent Sprague-Dawley rats may have as much as 35% of their body weight as dissectable adipose tissue (142). This increased adiposity results in an increased retention of the highly lipophilic environmental pollutants, polychlorinated biphenyls, in old as compared to young rats. An increase in the body burden of the volatile lipophilic solvent 1,1,1-trichloroethane (methyl chloroform) appeared due to an age-related increase in its Vd (143) in both rats and mice. In contrast, a decrease in Vd in old rats for ethylenediamine (144) and ethanol (145), both water-soluble agents, enhanced toxicity at a constant dose (on a body weight basis). Preliminary results from our laboratory indicate that benzene, a known carcinogen, is retained longer in older animals due to the increase in adiposity.

METABOLISM

Elimination of chemicals from the body can occur in two ways, biotransformation and/or excretion. Many water-soluble compounds can be excreted without being metabolized. However, for more lipophilic chemicals, metabolism to a more hydrophilic form is a prerequisite for excretion.

As with absorption and distribution, physiological changes that occur with aging can influence biotransformation reactions, both in the liver, the major site for the metabolism of drugs and environmental chemicals, and in extrahepatic tissues. Significant biotransformation reactions occur in all the portal-of-entry tissues (skin, respiratory tract, GI tract), as well as kidneys, gonads, endocrine organs, brain, and blood. Biotransformation can generally be considered to involve two types of reactions. Phase I reactions involve the addition of a functional group to the compound of interest, often leading to an increase in polarity. They include oxidation, reduction, and hydrolytic reactions. The product of a phase I reaction may be more or less toxic than the parent compound. Phase II reactions are often synthetic and involve the conjugation of functionalized molecules (either the parent compound or the product of a phase I reaction) with an endogenous substrate such as an amino acid, peptide, sugar, or small ion (methyl, acetate, sulfate groups). The choice of a phase II pathway often depends upon cofactor supply, with a functionalized molecule being able to react with several phase II substrates. Phase II reactions are usually thought of as detoxification processes, although in some cases further metabolism of a phase II conjugate may enhance toxicity (146). Phase I and Phase II reactions may occur either on cellular membranes or in the cytosol, depending on the pathway involved.

In addition to phase I and phase II enzymes, which are involved in the activation and detoxification of environmental chemicals, a third group of enzymes play a role in biotransformation by protecting cells and tissues against possible damage from active, oxidizing intermediates produced by metabolism. These antioxidant enzymes, including catalase, superoxide dismutase, and glutathione peroxidase, protect against oxidant stress, which may in and of itself contribute to the processes of aging (147, 148).

Any or all of these biotransformation reactions may change with age. However, few generalizations appear to hold, other than that metabolic changes with aging appear to vary with substrate, tissue, sex, strain, and species. In addition to intrinsic changes resulting from age-related changes in physiology and biochemistry, the study of aging and biotransformation is confounded by the effects of diet, alcohol, drugs, and other environmental chemicals (69). For example, while it is generally stated that drug metabolism in humans declines with age, this conclusion is based almost totally on studies with antipyrine (5).

Phase I reactions include the mixed-function oxidases (MFOs; monooxygenases), alcohol and aldehyde dehydrogenases, monamine oxidases, nitro- and azo-reductases, esterases, and amidases. The MFOs are a membrane-bound multienzyme system that insert one atom from molecular oxygen into the substrate and form water with the other. The prime electron donor is NADPH via NADPH-cytochrome P450 reductase to a terminal electron acceptor, cytochrome P450. The cytochromes P450 are a family of hemoproteins with overlapping substrate specificity. Lipid plays an obligate role in this system. While aging appears to lead to a decrease in phospholipid content in microsomal membranes, the functional significance of this is unclear since membrane physicochemical properties have been reported to change in opposite ways (149, 150) or remain unchanged (151) with age.

Conflicting data also exists concerning the NADPH-dependent reductase, with mostly decreases in activity or no change with age being reported (68). Recent studies have generally shown an age-related decrease in this enzyme in aging rat liver (152–155). In contrast, no decline in NADPH cytochrome P450 reductase activity was observed in the liver of aging Rhesus monkeys (156).

The total amount of cytochrome P450 appears to remain unchanged or decrease, although measurement of the total level may not be a very meaningful parameter. Recent studies have indicated that the decline, when detected, in total cytochrome P450 levels is due to the age-related decreases in the male-specific forms (157–160). In fact, Friedman et al (161) demonstrated that aging in male rats altered the composition of testosterone-binding cytochrome P450s. This change in isozyme composition is due to a decrease in circulating testosterone levels (162) and can be retarded by dietary restriction (163). Changes in cytochrome P450 isozymes appear much less pro-

nounced with age in female rats or in other species, although the age-related decline in the metabolism of antipyrine is greater in men than women (108). In contrast, although total levels of cytochrome P450 do not decrease in aging female rats, the metabolism of aniline, benzphetamine, and nitroanisole does decline in both sexes (155). This may reflect an age-related increase in heme degradation (163a). Thus, age-related changes, in addition to those occurring in the male-specific forms of cytochrome P450, appear to play a role in alterations in MFO activity. Paramanova & Dougi (164) have also reported changes in other cytochrome P450 isozymes in old rats. This supports the observation that in humans age can alter the profile of metabolites from the same parent compound (165).

The mixed-function oxidase system is sensitive to both endogenous and exogenous modulation. The relationship between aging and inducibility remains unclear (68), possibly because different isozymes of cytochrome P450 can be induced by different chemicals. Smoking appears to result in similar induction of antipyrine (166), theophylline, and cortisol (167) metabolism. Theophylline metabolism is equally inducible by cimetidine (168) and phenytoin in young and old men (167). These studies in humans are in agreement with recent studies of Rikans (169) indicating that ethanol and acetone have similar inductive properties in young and old rats. In contrast, Paramanova (170) reported an increase in latency of induction and a decreased inducibility by phenobarbital in aged rats. This decreased induction is apparently due to a decreased rate of transcription of the phenobarbital-specific isozymes in aging rat liver (171). One possible explanation for some apparent discrepancies in inducibility of monooxygenase activity with age may relate to age-related differences in the metabolism of certain modulators. For example, cimetidine is more effective at inhibiting metabolism of other compounds in old rats. This is due to its own decreased rate of metabolism, leading to higher concentrations of this inhibitor in the aged liver (172).

The effect of aging on the coordinated function of the hepatic MFO activity appears highly variable, possibly because of the complexity of cytochrome P450 isozymes. Using hepatic microsomes, Wynne et al (173) reported that maximal MFO activity decreased with age, with no change in apparent enzyme affinity. The metabolism of a single substrate, such as benzo(a)pyrene (BP), has been reported to increase (174), decrease (175–178), or remain unchanged (179, 180), depending on the sex, strain, and species examined. Aflatoxin metabolism in aging liver appears to decrease (178), while that of dimethylnitrosamine remains unchanged (181) or decreases (182). Hepatic metabolism of 2-aminofluorene may either increase (183) or decrease (184) while the metabolism of the closely related compound, 2-acetylaminofluorene, decreased (184, 185) or remained unchanged (181). The metabolism of three liver tumor promoters, phenobarbital (186, 187),

2,2',4,4',5,5'-hexachlorobiphenyl (142), and lindane (188) also decreased with age.

The MFO metabolism of several alkylhalides has been observed to decrease with age. DiRenzo and coworkers (189) noted a decline in senescent animals in the bioactivation of ethylenedibromide, carbon tetrachloride, chloroform, and 1,1,2-trichloroethane. Recent studies (190) with methylene chloride indicate an age-related decrease in its rate of metabolism. In contrast, older rodents appear to metabolize 1,1,1-trichloroethane more rapidly than younger animals (143). Oxidative metabolism of salicylate at high doses appears to preferentially increase in old as compared to young rats (191). In contrast, metabolism of bupivacaine (192), p-nitroanisole (193, 194), hexobarbital (129), and haloperidol (195) all decline in old rats.

Age-related changes in extrahepatic MFOs have not been examined in detail, but also appear to be substrate-, sex-, strain-, and species-specific. Pulmonary metabolism of benzo(a)pyrene has been reported to increase with age (177, 160), while oxidation of aminofluorene by the lungs decreases (184). No age-related change was noted in pulmonary activation of aflatoxin B_1 or acetylaminofluorene (184).

Age-related changes in renal MFO activity have been examined for several substrates. Aflatoxin metabolism may either decrease (196) or remain unchanged (184). The activation of both acetylaminofluorene (184) and aminofluorene (184, 196) decreases in aging rodent kidney. Renal oxidative metabolism of acetaminophen decreases with age (197), while that of salicylate remains unchanged (198). Metabolism of BP is greater in the aging rat kidney (160).

Intestinal MFO activity alterations with age may reflect regional differences. Colonic metabolism of BP (160) is elevated in old as compared to young rats. A similar situation exists for the oxidation of dimethylhydrazine in elderly people (199). In contrast, no age-related change was observed in the metabolism of BP by the small intestine (200).

No data are available on age-related changes in skin, adrenals, or other tissues with significant levels of MFO activity.

Age-related changes in phase I enzymes other than the MFOs have been examined in much less detail. Rikans & Moore (201) observed a male-specific increase in liver alcohol dehydrogenase in rats, confirming earlier work (202, 203). The oxidation of ethylene glycol monobutyl ether (2-butoxyethanol) to butoxyacetic acid increases with age (204), probably due to an increase in alcohol dehydrogenase. In contrast, Hahn & Burch (205) reported a decline in alcohol dehydrogenase in livers from old rats. No change was seen in colonic alcohol dehydrogenase (200).

Some attention has been paid to both plasma and tissue esterase activity during aging. The hydrolysis of diethylhexylphthalate decreased in old liver,

but remained unchanged or even increased in lung and kidney (206). Hydrolysis of benzylacetate to benzyl alcohol by plasma esterases appears to decline with age in both rats and mice (207). No change was observed in brain acetylcholinesterase or in serum or liver aliesterase in mice (208). Rhodanase activity declines in aging brain, but not liver, suggesting a basis for the enhanced sensitivity to cyanide toxicity observed with age (209). No reports on other phase I enzymes in liver or extrahepatic tissues have appeared.

Less is known generally about the effects of aging on phase II conjugation enzymes. Conventional wisdom holds that age has little effect on phase II reactions, at least in humans (70). However, since these enzymes are also very substrate-, sex-, and species-variable, such a conclusion may not be warranted. For example, acetylation has been reported to decline in the elderly (210).

Glucuronidation is often considered the most important conjugation pathway. Multiple isozymes exhibit differential substrate specificity and inducibility. Different investigators have observed hepatic glucuronidation of acetaminophen and estrone to increase (193, 211, 212) or remain unchanged (213, 214) with age. While no effect of aging on the glucuronidation of naphthol, paranitrophenol, and testosterone was reported by Galinsky et al (193) and Sweeny & Weiner (194), many other investigators (174, 214–218) have observed a marked decrease in the conjugation of these substrates by the liver. The glucuronidation of 2-aminophenol, 4-hydroxytryptamine, and bilirubin (214), and morphine (193) appears not to change with age, while that of 4,4'-thiobis-(6-t-butyl-m-cresol) (215), chloramphenicol (218), and androsterone and tetrahydrocortisone (214) decreased. Glucuronidation of lindane (188) and benzoic acid (207) appears to increase with age.

Extrahepatic glucuronidation has been examined with age in several tissues. Glucuronyl transferase activity decreased in the aging kidney (213, 215). Glucuronidation of paranitrophenol appeared unchanged with age in the lung and small intestine (215), but decreased in the colon (200), while conjugation of 4-methylumbelliferone increased in the same tissue (219). Thus, the activities of glucuronyl transferase are highly variable, probably reflecting compositional changes in the isozyme profile. However, the levels of the required cofactor, UDP-glucuronic acid, decline in both liver and kidney (220), suggesting that regardless of the inherent enzyme activity, glucuronidation could be limited in older animals. Enhanced levels of functionalized compounds may also be predicted given the age-related increase in the enzyme that hydrolyzes the conjugates, β-glucuronidase (215, 221, 222).

While glucuronidation is often considered a high-capacity, low-affinity pathway, sulfation usually involves low-capacity, high-affinity reactions. At least two sulfotransferases respond differentially to aging (223). Sulfation of phenolic substrates appears to decline with age (193, 194, 211, 212), while

conjugation of sulfate with bile salts, androsterone, corticosterone, lindane, and paranitrophenol increases (194, 188, 214, 216). No change in the sulfation of β-napthol or estrone has been observed with age (214, 218). No studies have yet examined whether or not the availability of PAPS (adenosine 3'-phosphate-5'-phosphosulfate), the required cofactor for sulfation, changes with age.

The concentration of hepatic glutathione, the cofactor involved in the third major class of conjugation reactions, has been reported to increase (224, 225), decrease (226, 227), or remain unchanged (218, 228–230) in old rodents. While Lang et al (231) have suggested that glutathione levels decline in all tissues during senescence in a wide range of species, the only tissue in which Rikans & Moore (230) observed a decrease was the lens of the eye. Several investigators (197, 201, 225, 229) have, in fact, reported increases in renal glutathione levels. Colonic glutathione levels remain constant (200) with age.

The variability reported in the effects of aging on glutathione concentration is repeated in apparently conflicting results concerning age-related changes in glutathione-S-transferase (GST) activity. As with the other biotransformation enzymes, GST represent a family of isozymes with overlapping substrate specificities. The isozymes are either homo- or hetero-dimers, involving at least six distinct peptides. Spearman & Leibman (228) observed that aging selectively alters the GST isozymes in rat liver as opposed to lung. These changes were substrate-, sex-, and tissue-specific. Glutathione conjugation with sulfobromophthalein decreased in old male, but not female, rat liver (232). In fact, age-related declines in GST activity tend to be male-specific in rats (233), similar to that observed for the change in cytochrome P450. Colonic conjugation of 1-chloro-2,4-dinitrobenzene decreases (200), while its reaction with glutathione in the heart (153) and liver shows no effect of aging (178, 193, 228, 233). In contrast, glutathione conjugation with this substrate increases in the brain of old rats (153). Conjugation of 1,2-dichloro-4-nitrobenzene appears to decline with age in both males and females (178, 226).

Age-related changes in glutathione conjugation of acetaminophen have been intensively examined since it is a major pathway of detoxification of the reactive oxidative intermediate. Sweeny & Weiner (212) reported that hepatic conjugation of acetaminophen with glutathione did not change in aging rats or mice. This would be in agreement with the lack of enhanced acetaminophen hepatotoxicity in old rats (234). In contrast, renal glutathione conjugation of acetaminophen decreases (197). A lack of alteration in glutathione conjugation of various substrates with age in the liver has been observed by numerous other investigators (180, 214, 218, 224, 225). This heterogeneity, however, is supported by reports of increased glutathione conjugation with a variety of substrates (214) vs decreases (182). Conjugation with glutathione is the first

step in the pathway of mercapturic acid synthesis. A later step, cleavage of the glutamic acid residue by gamma glutamyl transpeptidase, has recently been reported to increase with age (214).

Other phase II pathways have been less extensively examined for the effects of aging. Epoxide hydrolyase catalyzes the addition of water to an epoxide to form a diol. There are at least two forms of this enzyme, one membrane-bound and one cytosolic. Depending on the substrate used, which may reflect isozyme specificity, hepatic epoxide hydrolase activity has been reported to both increase (218, 224) and decrease (180, 214, 235) with age. Chengelis (218) has suggested that these apparent discrepancies may be due to a gradual increase throughout most of the lifespan followed by a drop during extreme old age. Kaur & Gill (235) observed a substrate-dependent decrease in epoxide hydrolase activity in lung, small intestine, and kidney, supporting the differential effects of aging on different isozymic forms.

Neither acetylation nor deactylation has been examined in great detail as a function of age. Acetylation has been reported to decline in the liver both in humans (236) and rats (214). Renal acetylation appears to decrease with age (237). However, since the product concentration is often determined by a balance between conjugating and deconjugating enzymes, the balance between acetylation and deacetylation needs to be examined. Recent reports suggest that deactylation of acetaminophen, at least in the kidney, remains unchanged with age (197) or slightly decreases (213).

The remaining major phase II pathway that has been examined for the effect of aging involves conjugation with glycine. This is a complicated three-step pathway, predominantly within mitochondria, that involves activation to an acetyl-CoA thioester followed by reaction with glycine. Stern et al (238) observed a decreased ability of aging humans to form hippuric acid, the glycine conjugate of benzoic acid. They attributed this to a decline in glycine availability. In contrast, recent studies by McMahon et al (207) observed no effect of age on the formation of hippuric acid in vivo in rats or mice. Another substrate for which glycinc conjugation represents a major detoxification pathway is salicylate. In humans, several studies have indicated that the formation of salicyluric acid, the glycine conjugate of salicylate, is not changed with age (239–241).

In contrast, Montgomery & Sitar (242) reported elevated levels of this glycine conjugate in plasma from elderly people in agreement with the observation that salicyluric acid formation is actually increased in old rats (191). This may be due to an increase in the ability of N-acyltransferase to conjugate glycine with acetyl-CoA-salicylate. The decreased formation of salicyluric acid in aging rats reported by Kyle & Kocsis (198) was most likely the result of overt toxicity resulting from the high doses used. It may also reflect the dose-dependent shift away from glycine conjugation (191), since this appears to be a high-affinity, low-capacity pathway.

The effect of aging on the enzymes that protect against oxidative stress has not received much attention. While the age-related changes in glutathione content are species- and tissue-dependent, the enzyme glutathione peroxidase, which oxidizes glutathione while reducing hydroperoxides, appears to decline in liver, kidney, heart (242a), and colon (200). This would suggest a decreased detoxification of hydrogen peroxide and lipid peroxides during senescence. Lungs of aged rats appear more sensitive to oxidant stress induced by ozone due to an inability to maintain the ratio of NADPH/NADP (243).

Superoxide dismutase (SOD) reduces the superoxide anion, preventing the production of oxygen-derived free radicals. The activity of this enzyme decreases in liver from aging rodents (244–247). This is due to a decreased synthetic capacity resulting from a decline in gene expression (247). Catalase activity, which converts hydroxyl radicals to water, also declines in aging liver (247–250). This is also due to decreased transcription of these genes into mRNA. Thus, the age-related decrease in the expression of SOD and catalase could increase the susceptibility of older animals to free radical damage.

EXCRETION

Excretion leads to the elimination of the chemical and/or its metabolites from the body. Of the three major routes of excretion, the kidney is the prime excretory organ, with the liver and lungs also serving important roles in this process. In addition, minor routes involve hair, sweat, saliva, and sex-linked processes such as lactation. For certain classes of chemicals, these routes may play a major role in reducing the body burden. Clearly, lactation does not occur during senescence. For the other minor excretory pathways, little is known about age-related alterations, although hair growth does change with age.

The pulmonary route is extremely important in the elimination of gases and volatiles, whether they are the original chemical of exposure, for example a volatile anesthetic or solvent, or a product of metabolism, such as carbon dioxide or carbon monoxide. This excretory process depends upon the age-related changes in pulmonary physiology (77) and affects excretion just as it did pulmonary absorption. For example, while a decreased rate of respiration may slow absorption, it also impedes exhalation. Age-related changes observed in the pharmacokinetic behavior of 1,1,1-trichloroethane were in part related to a decreased rate of pulmonary elimination (143). While the cardiac index decreases as a function of age, the apparent fraction of cardiac output reaching the lungs increases (92), resulting in implications for the elimination of blood flow-limited gases.

While the lung functions as both an organ of absorption and elimination, the major function of the kidney is elimination of wastes from the body.

Age-related impairment of renal function has long been known (251–253). Much of the age-related decline is due to a reduction in blood flow to the kidney (127) resulting in a lower rate of glomerular filtration. The number of functional nephrons declines in direct proportion to the glomerular filtration rate. Tubular secretion and resorption are also reduced in the elderly. Taken together, these changes suggest that the nephron loses its function as a unit (254). Thus, the effects of age on renal function appear to play a major role in alterated pharmacokinetics in the elderly (255, 256). Decreases in renal clearance result in increased persistence or concentration of chemicals in the body, potentially leading to toxicity (163). In humans, decreased renal clearance in the elderly has been demonstrated for many major therapeutic drugs, including various aminoglycosides, tetracycline, lithium, digoxin, procainamide, methotrexate, and phenobarbital (257). Renal elimination of digoxin (258), a major metabolite of procainamide, N-acetylprocainamide (259), and 2-acetylaminofluorene (185) also decreases in aging rodents.

The kidneys of aging rodents are extremely susceptible to chronic glomerulonephropathy (260, 261). Recent studies have indicated that much of this may be a consequence of diet (25). Altered glomerular morphology, characterized by thickening of the basement membrane and sclerosis, gets progressively worse, increasing in severity with advancing age, and eventually resulting in scarring and actual nephron loss.

Renal tubules are also subject to degenerative changes. These changes are accompanied by proteinuria, especially an increase in albumin (262, 263). The increase in urinary protein appears as a consequence of the age-related increase in glomerular permeability as well as a loss of fixed glomerular polyanion (264). The increase in albumin may represent nonselective leakage of large proteins into the urine due to increased glomerular permeability, since the protein concentration in urine approaches that of the plasma (265). Of course, albumin synthesis also increases during senescence (64).

Additional changes occur in the tubules of aging kidneys. These are frequently hyperplastic and degenerative, resembling pathology seen as a response to specific environmental chemicals (266). Proximal tubular organic anion transport declines with advancing age (237, 261). Galinsky & Corcoran (211) have demonstrated an age-related decline in the active transport of acetaminophen-sulfate out of the kidney, with no effect on the secretion of acetaminophen-glucuronide, suggesting that age-related changes in renal elimination may be substrate-specific, just as are metabolic changes. The renal transport of butoxyacetic acid decreases with age (267) as does that of cephaloridine (60), in both cases contributing to enhanced nephrotoxicity during aging. Decreased tubular transport may be a function of diminished turnover of the sodium/potassium ATPase in aging proximal tubules (268).

Hepatic elimination may also be compromised by aging since a number of

hepatobiliary functions have been reported to decline with age. Like the kidneys, reduction in blood flow (92, 269) plays a major role in reduced elimination in the liver. Kitani (162) has suggested that the age-related decline in the excretory capacity of the liver is due to functional alterations in the hepatocytes. In fact, the relative number of hepatocytes decreases with age as does the relative liver weight (64). Bile flow is reduced with age in male rats (220, 232), but not in female rats (270), suggesting another age-related change exhibiting sexual dimorphism. Biliary transport also declines, especially with polar compounds such as sulfobromopthalein (232). The biliary excretion of the neutral, but polar, glycoside, ouabain, decreased with age in both male and female rats (271). In contrast, aging has less of an effect on the biliary elimination of digoxin and digitoxin, which are less polar (272). The functioning of the biliary canalicular transport system steadily declines during aging (273).

Some of the alterations in biliary elimination with age may be due to age-related changes in hepatic uptake as well as in bile flow and transport (274). Zs-Nagy and coworkers (275) have suggested that all these effects may be due to alterations in the hepatocyte plasma membrane. These experimental observations are relevant to the situation in elderly people where biliary excretion as well as bile acid synthesis has decreased (276).

CONCLUSION

It is clear that the pharmacokinetic behavior of environmental chemicals and drugs is, in many cases, altered during aging. Absorption may be the least sensitive parameter to age-related perturbations. However, pulmonary and dermal absorption, which are both dependent upon passive diffusion, do appear to decline. In contrast, no evidence supports a decrease in passive transport across the gut wall, while active processes in the GI tract do decline in the aged. Distribution is affected by changes in body composition, the decrease in lean body mass resulting in a decreased Vd for water-soluble chemicals and enhanced persistence of lipophilic ones. Changes in protein binding and blood flow also alter the concentration of unbound chemicals reaching the target site. The changes in metabolism are extremely complex, with increases, decreases, and no change being observed for different enzymes with varying substrates in different tissues, sexes, strain, and species. Only excretion tends to consistently change with age, in large part due to the altered blood flow, structure, and physiology of the kidney. Hepatic and pulmonary elimination also tend to decline with age.

No broad generalizations can be made about pharmacokinetic changes with age, other than that alterations may occur. Of course, what is meant by "age" must always be clearly defined. Age-related comparisons should be made

between young adults and organisms at, or at least approaching, the mean life span of their populations (68, 277). Such senescent changes can lead to altered sensitivity to chemicals, whether drugs or environmental agents, in the aged. For example, the enhanced production of reactive oxidative metabolites of salicylate in the elderly may play a major role in the increased susceptibility of the aged to salicylate-induced nephrotoxicity (191). Older mice appear more sensitive to the neurotoxic properties of cyanide because of a decrease in brain rhodanase (209). Age-related changes in the renal cortical accumulation of cephaloridine contribute importantly to its age-dependent renal toxicity (278). Changes in the Vd lead to enhanced toxicity of ethylenediamine (144). Decreases in the active tubular secretion of butoxyacetic acid lead to elevated blood levels and enhanced hematotoxicity (267).

Thus, alterations in pharmacokinetic parameters in the elderly may well lead to a population at special risk from the toxic effects of both drugs and environmental chemicals.

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